Clinical validity and utility of genome profies in risk assessment and control of CRC

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Goals of this meeting

Clinical goal:

Can “genome profiles…. assess individual risk for disease based on the combination of genetic variation at multiple loci.”

Scientific goal:

What “scientific foundation for using personal genome files for risk assessment, health promotion and disease prevention.”

Focus: “actionable information”

CRC Prevention Background

CRC in USA

- 150,000 cases/yr
- 50,000 deaths/yr

Risk over lifetime

- M: 5.7% incidence (2.3% death)
- F: 5.2% (2.1%)

Other

- 90% of CRC occur >50y.o.
- Only 1/3 detected at ‘curable’ stage
- adenomatous polyp common (30-50% >50y.o.)
- chemoprevention has limited role

CRC Prevention: What clinical questions and what kinds of 'risk'; can genomics help

Clinical questions

1. What risk of CRC *over lifetime*?
2. What risk of CRC *now*?
3. What risk of CRC *in future,* over next X years?
   (e.g., after colonoscopy/polypectomy)

CRC Prevention: What clinical questions and what kinds of 'risk'; can genomics help

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For each question, consider:

- importance
- current approach (actions based on risk)
- potential of genomics

1. What risk of CRC *over lifetime*?

There are 3 risk groups:

- High
- Average
- Low

1. What risk of CRC *over lifetime*?
High Risk (e.g., APC/FAP)

Definition
- autosomal dominant (chrom. 5); small N

Importance
- biology: elucidate biology of ‘common CRC’
- clinical: ~get CRC in 20s

Approach
- colectomy; action based on FH (though few have no FH), sigmoidoscopy

Potential of genomics in 2008
- limited

1. What risk of CRC *over lifetime*?
Average Risk

Importance
- big N

Approach:
- screening (early detection)
  - •colonoscopy, FOBT, sigmoidoscopy
  - •screen >age 50
  - •target: ‘early CRC’, ‘advanced adenoma’

Potential of genomics in 2008
- sort out, among ‘average’, who has higher/lower risk (‘tailoring’)

1. What risk of CRC *over lifetime*?
Average Risk

We already do some ‘tailoring’ in CRC screening.

What lessons?

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Average Risk

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What lessons?

How do we manage ‘family history’?

Risk is, roughly, 2x ‘normal’.

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Average Risk

We already do some ‘tailoring’ in CRC screening.

What lessons?

How do we manage ‘family history’?

Tailoring is based not on ‘genomics’, but genomics would give same kind of information about risk.

Family history: It's a gigantic mess.

Table summarizes different groups' recommendations

Variable	USPSTF[2] (1996)	Consortium guidelines[4] (1997)	American College of Gastroenterology[60] (2000)	American Cancer Society[62] (2001)	USPSTF[63] (2002)	guidelines (US Multisociety Task Force on Colorectal Cancer)[64] (2003)
If affected relative with CRC is older						
Increased risk is indicated by	If single FDR, it is not clear that the modest increase in risk justifies routine use of colonoscopy over other screening methods	If close relative with CRC	Single FDR with CRC over age 60 y	If relative is over age 60, person is average risk	Silent	FDR with CRC over age 60 y or 2 second-degree relatives
What action	Routine screening as for average risk	Routine screening as for average risk; start age 40 y	Start age 40 y colonoscopy every 10 y	Routine screening as for average risk	Silent	Routine screening as for average risk; start age 40 y
If affected relative with CRC is younger						
Increased risk is indicated by	When affected relatives are younger may justify beginning screening before age 50 y	If relative had CRC before 55 y or adenomatous polyp before age 60 y	Single FDR with CRC under age 60 y or multiple FDRs with CRC	Single FDR under 60 y or 2 FDRs, any age	FDR under age 60 y	FDR with CRC under age 60 y
What action		Make special efforts to ensure that screening takes place	Start age 40 y or 10 y younger; colonoscopy every 3–5 y	Total colon examination (TCE) age 40 y or 10 y before youngest case then TCE every 5–10 y	Initiating screening at an earlier age is reasonable	Colonoscopy every 5 y starting at age 40 or 10 y younger
If relative has adenomatous polyps						
What action	Same as for CRC	Same as for CRC	Issue has not been studied adequately	Same as for CRC	Silent	Same as for CRC

NOTE. Recommendations for screening based on family history vary substantially at several levels. One difference concerns the type of family history that indicates increased risk. Is 1 FDR sufficient or 2? Other differences concern how the age of the relative may affect risk. Last, if risks are increased, there are differences regarding what kinds of tests should be performed (regular screening tests such as FOBT and sigmoidoscopy

From Ransohoff D. Gastroenterology 2005;128:1685-95

Family history: It's a gigantic mess.

Recommendations reflect disagreement at every level:

a. What *is* degree of risk, and what features *indicate* risk?
1 FDR; >1 FDR; age?

b. What degree of risk warrants 'action'?

c. At that degree, *what action*?
- more 'intense' test (e.g. colonoscopy)
- same testing program as for average risk but earlier age
- more frequent testing program

d. Does FH of adenoma mean same thing as FH of CRC?

The 'problem' in a-d:

insufficient data; disagreement about what data mean

What lessons from family history: from 30,000 feet

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Yes we have very little data. But even if we had data, we have *no quantitative conceptual framework* to handle:

a. What *is* degree of risk?

b. What degree of risk warrants ‘action’?

c. At that degree, *what action*?

Does this kind of framework exist for other cancers; can it be applied to CRC?

Quantitative conceptual framework: can it help in CRC?

Before we develop framework, consider whether it will provide ‘actionable’ information:

- In USA, CRC screening is over-used (compared to what prescriptive quantitative decision-making says):
  -too-frequent follow-up after a normal, or polyp

  In other words, many people who are getting screening are getting too much.
- Pressures to over-use colonoscopy: relatively safe; ‘everyone benefits’ by being aggressive.
- Would better quantitative information about risk (e.g. genomics, tailoring) make a difference?

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Here is one kind of data that – if it exists – *could* provide important actionable information:

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Is there a *very low risk* group?

- **Lifetime risk *so low* that screening not needed.**

Would better information (e.g. genomics) make a difference?

Here is one kind of data that – if it exists – *could* provide important actionable information:

Is there a *very low risk* group?

- **Lifetime risk *so low* that screening not needed.**

I.e. Rather than ‘tinker’ with different degrees of ‘high risk’ (because people are already getting aggressive screening) can we identify 50% or 20% of population *with very low risk?*

Can we identify 50% or 20% of population with very low risk?

From J Gulcher

What does CRC curve look like? On left, a *very low risk group?*

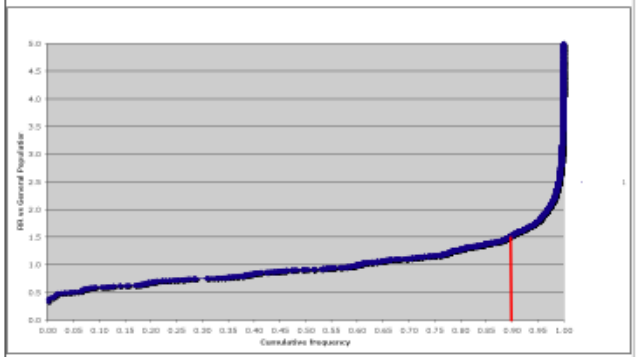
Developing drugs and diagnostics for common diseases

Genetic Risk Tests Already Available for Common Diseases

Helping physicians prevent or detect earlier some of the most important common diseases

Jeff Gulcher MD PhD
CSO and co-Founder
Decode Genetics

8 validated genetic markers defines Prostate Cancer risk ranging from 0.4 to 6 fold



Can we identify 50% or 20% of population with very low risk?

Comment:

a. I don’t expect Mother Nature works this way, but I’m not genetics person; what do you think.

b. But I can tell you that, if MN does work this way, this would be important/actionable information.

CRC Prevention: What clinical questions; what kinds of 'risk'; can genomics help

Clinical questions

1. What risk of CRC *over lifetime*?
2. **What risk of CRC *now*? (e.g. screening)**
3. What risk of CRC *in future,* over next X years?
   (e.g., after colonoscopy/polypectomy)

2. What risk of CRC *now*?

Importance

Identifying ‘risk now’: goal of screening, early detection.

Examples of screening tests

- at present: colonoscopy, FOBT, sigmoidoscopy
- in (near) future: virtual colonoscopy
- in (distant/never?) future: serum proteomics;
  serum genomic (cancer cells or DNA in blood; other)

Potential for genomics in 2008

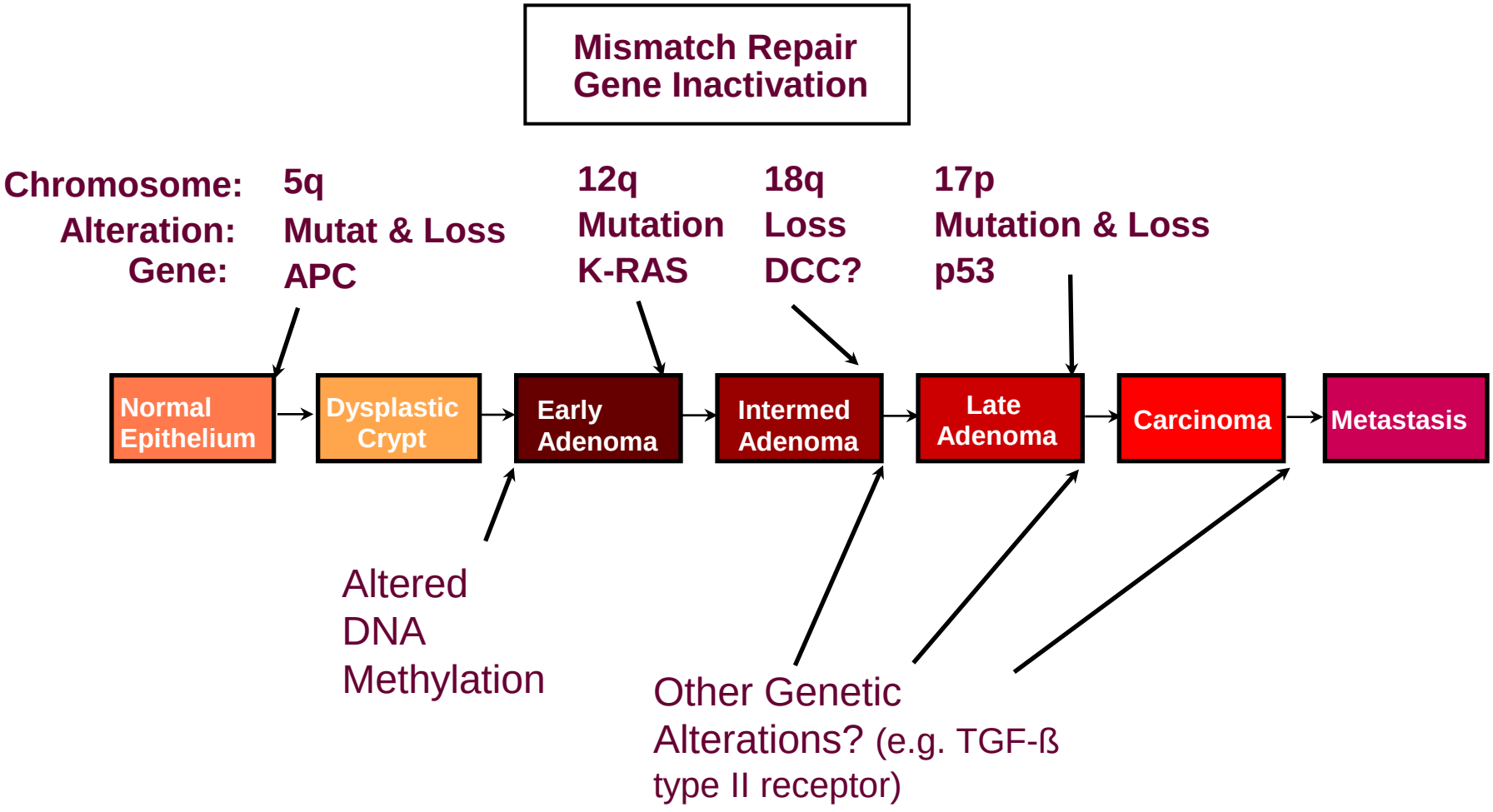
2. What risk of CRC *now*?

Potential for genomics in 2008

One example with lessons:

DNA mutations in stool (shed CRC cells) – is this be basis for detecting CRC now (screening)?

Biological rationale: Vogelstein's description of genotype/phenotype progression



Modified from Fearon and Vogelstein Cell 1990; 61:759-767

2. What risk of CRC *now*?

Working with Vogelstein, EXACT Sciences developed a way to measure human DNA in stool:

- APC
- Kras
- p53

Can stool DNA test detect CRC?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fecal DNA versus Fecal Occult Blood for Colorectal-Cancer Screening in an Average-Risk Population

Thomas F. Imperiale, M.D., David F. Ransohoff, M.D., Steven H. Itzkowitz, M.D.,
Barry A. Turnbull, Ph.D., and Michael E. Ross, M.D.,
for the Colorectal Cancer Study Group*

NEJM 2004;351:2704-14

(Disclosure: DFR was consultant/chair of EXACT SAB until 2002)

Can stool DNA test detect CRC?

Answer:

1. Yes, but not well: sensitivity 51%; specificity 95%
    - a lot better than fecal occult blood testing
    - but test is expensive
2. SO can biological approach be improved?

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Mother Nature fools us again!

Goals of this meeting: what *research agenda for CRC*

Clinical goal:

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Scientific goal:

What “scientific foundation for using personal genome files for risk assessment, health promotion and disease prevention.”

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Goals of this meeting: what *research agenda for CRC*

1. Is field of CRC prevention 'ready' for genomic information about risk?
   - no quantitative conceptual framework
   - 'family history' situation illustrates not only lack of data, but also lack of framework to handle it
2. HOWEVER, one potential use of genomic information about lifetime risk that is clinically important:
   - *Can a **low-risk** group be identified that does **not** need screening?*

This potential use is neat, clean, clinically important

This potential use is: neat, clean, clinically important

.. and meets Khoury criteria ***(Genomics 2008)***

‘Evaluation focus,’ ‘clinical validity,’ ‘clinical utility’

EXHIBIT 1
Domains In The Evaluation Of Genomic Applications Proposed For Clinical Practice

Domain	Element
Evaluation focus	Definition of the disorder/test/clinical scenario or intended use (for example, population tested, diagnostic or predictive)
Analytic validity (A)	Analytic sensitivity, specificity, predictive values, reliability and robustness
Clinical validity (C)	Gene-disease associations; clinical sensitivity, specificity, predictive values
Clinical utility (C)	Efficacy, effectiveness, safety, acceptability, efficiency, feasibility of implementation, costs
Ethical, legal, and social issues (E)	Confidentiality, privacy; access, stigmatization, discrimination

SOURCE: Adapted from J.E. Haddow and G.E. Palomaki, "A Model Process for the Evaluating Data on Emerging Genetic Tests," in *Human Genome Epidemiology: Scope and Strategies*, ed. M.J. Khoury, J. Little, and W. Burke (New York: Oxford University Press, 2004), 217–233.

EXHIBIT 2
Characteristics Associated With Low And High Evidence Thresholds For Genomic Applications In Practice

Characteristic	Low threshold	High threshold
Analytic validity	Laboratory certification Validation data required	Regulatory oversight Systematic review of data
Clinical validity	No or limited data required	Systematic review
Clinical utility	No data required	Systematic review
Clinical guidelines	Expert opinion/professional guidelines	Evidence-based recommendation by independent group
Coverage and reimbursement	Highly variable	More consistent

SOURCE: A thorough review of processes of the current oversight system for genetic testing in the United States is provided by the Secretary's Advisory Committee on Genetics Health and Society, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, April 2008, http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf (accessed 6 June 2008).
NOTE: For explanation of low versus high thresholds, see text.

end